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ORIGINAL RESEARCH

Frequency of Severe Asthma and Its Clinical Phenotypes at the Asthma Clinic in One of the Largest Sudanese Tertiary Pediatric Hospitals: A Cross-Sectional Hospital-Outpatient-Based Study

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Background: Asthma is one of the most common non-communicable diseases. Childhood asthma has been increasing in Sudan, with a 13–16% prevalence among Khartoum school children. To achieve and maintain good asthma control, proper diagnosis, assessment of severity, and appropriate medication administration are crucial, with phenotyping being a key factor in determining patients' specific treatment.

Objective: To study the frequency of severe asthma and the distribution of its different phenotypes and to investigate associations between age and gender and different phenotypes of asthma.

Methodology: This descriptive cross-sectional hospital-based study was conducted in the Asthma Clinic of Mohamed Al-Amin Hamid Pediatrics Hospital. It included 229 patients who were presented to the clinic from September 2021 to April 2022. Data were collected from the patients and/or their caregivers using a modified validated standard questionnaire and were analyzed using SPSS version 26.0. A p-value of 0.05 or less was considered statistically significant.

Results: In this study of 229 participants, 14.4% had severe asthma, with 44.5% and 41% exhibiting mild and moderate asthma, respectively. Most were effectively managed in steps 2 or 3. The cohort, primarily aged 5 or younger (40.2%) with a male majority (62%), showed a mean diagnosis age of 2.9 ± 2.8 years. Impressively, 90% maintained well-controlled asthma. Within severe asthma cases (87% atopic), 39.4% represented a severe allergic asthma phenotype. Elevated eosinophil counts were noted in 45.5% (serum) and 78.8% (sputum cytology), while 57.6% had normal serum IgE levels. The predominant symptom pattern in severe asthma was episodic multi-trigger wheezing (48.5%). Age and gender displayed no significant association with severe asthma phenotype.

Conclusion: This study reveals a concerning rise in childhood asthma prevalence in Sudan, emphasizing the importance of tailored treatment strategies. Severe asthma, characterized by atopic eosinophilic involvement, necessitates targeted interventions in pediatric asthma care for specific phenotypes.

Keywords: asthma, pediatrics, respiratory system, chronic obstructive pulmonary diseases, Sudan

Introduction

Asthma is a serious global health problem that affects an estimated 300 million individuals worldwide.[1] It is defined as a clinical syndrome of intermittent respiratory symptoms triggered by viral upper-respiratory infections, environmental allergens, or other stimuli, and is characterized by nonspecific bronchial hyper-responsiveness and airway inflammation.[2]

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The prevalence of childhood asthma has been reported to vary between 1% and 30% in different populations and is under-estimated and under-diagnosed in tropical countries.[3] The cause of asthma in children is unknown. A combination of environmental exposures and inherent biological and genetic susceptibilities have been implicated in the susceptible host's immune responses to common airway exposures (eg, respiratory viruses, allergens, tobacco smoke, and air pollutants), stimulating prolonged, pathogenic inflammation and aberrant repair of injured airway tissue.[4,5] A study to determine the burden of severe asthma in 3 countries in East Africa, Uganda, Kenya, and Ethiopia revealed that the prevalence of severe asthma and severe refractory asthma was 25.6% and 4.6%, respectively.[6] The three African nations with the greatest rates of childhood asthma prevalence, South Africa (20.3%), the Congo (19.9%), and the Ivory Coast (19.3%)— have rising rates of urbanization.[7]

At least 400,000 people died prematurely from asthma in 2016, mostly in low- and middle-income countries (LMICs) in Africa, according to estimates from the Global Burden of Disease collaboration. A survey carried out by the Global Asthma Network (GAN) in 2013–2014 revealed that several African nations lacked a national asthma strategy for adults and children, suggesting the lack of health promotion initiatives aimed at increasing public knowledge of asthma and its contributing factors.[8] In Sudan, asthma is a common disease that has high morbidity, and economic costs. It affects 12.5% of children and 10% of adults.[2,3] It caused 461,000 deaths worldwide in the year 2018, and 2639 (1.04% of total deaths) in Sudan, according to WHO data.[2] While extensive research exists on its prevalence and impact, there remains a notable gap in understanding the clinical phenotypes of asthma in children in Sudan. Despite the high morbidity rates and economic costs associated with asthma in the region, there is a dearth of studies addressing the specific factors influencing asthma severity among Sudanese children.[3] Asthma also affects the daily life of children, as it accounts for more school absences and hospitalizations than any other chronic illness.[9] It causes self-imposed limitation of physical activities, general fatigue and difficulty keeping up with peers in physical activities.[10,11] As for the new classification of asthma apart from phenotypes, asthma is classified into mild, moderate, and severe. This classification is based on response to treatment and is one of the most common and widely used classifications.[12] Mild asthma is defined as asthma responsive to step 1 or step 2 management.[12] Moderate asthma is responsive to step 3 management.[13] Severe asthma requires step 4 or 5 management, or asthma that remains uncontrolled despite treatment.[14] Omalizumab medication may be beneficial for patients with severe asthma apart from the optimal treatment.[15] Omalizumab restricts the binding of free serum IgE to the FcεRI receptor on the surface of basophils and mast cells. The particular inflammatory response brought on by effector cell activation during the allergen contact is reduced as a result of this inhibition.[16]

To our knowledge, there are no published studies that estimate the clinical phenotypes of asthma in children, or the factors that affect this severity in Sudan. This study aims to address this research gap by investigating the frequency of severe asthma and exploring the distribution of its various phenotypes. Additionally, the research seeks to identify potential connections between age, gender, and the different types of asthma.

Methodology

Study Design and Setting

This descriptive cross-sectional hospital-outpatient-based study was conducted at the Asthma Clinic within the Mohamed Al-Amin Hamid Pediatric Hospital in Eastern Omdurman, Khartoum. The clinic, situated in one of Sudan's largest pediatric hospitals, consists of a reception, and a waiting room for patients and caregivers, and is equipped with a screen for educational videos.

Study Population and Period

The study included all patients visiting the Asthma Clinic from September 2021 to April 2022. Patient referrals were received from both private and public hospitals within and outside Khartoum state.

Participants and Exclusion Criteria

The study population comprised patients clinically diagnosed with bronchial asthma and undergoing prophylactic treatment for at least three months. Exclusions were made for patients with coexisting conditions affecting asthma

severity classification (eg, congenital heart disease, gastroesophageal reflux disease), and those with factors impacting asthma control (eg, poor inhaler techniques, exposure to persistent environmental triggers, poor compliance).

Sampling and Data Collection

Convenience sampling was employed, resulting in a sample of 223 patients. A modified standard questionnaire served as the data collection tool. The questionnaire underwent a rigorous self-validation process, including expert consultations, pilot testing and cognitive interviews ensuring its reliability and alignment with the research objectives. It aimed to categorize patients into mild, moderate, and severe asthma. It gathered demographic data, independent variables (age at diagnosis, MBI, exposure to second-hand smoking, family history of asthma, assessment for associated atopic conditions), and clinical and laboratory assessments (serum and sputum sampling) for severe asthma phenotyping.

Data Analysis

Data analysis was conducted using SPSS Version 21®, employing descriptive statistics such as frequencies (%) and mean (SD) for categorical and numerical variables, respectively. The results were presented in tables. Normality was assessed using Kolmogorov–Smirnov statistics. Categorical variables were analyzed using Chi-square or Fisher's exact test as appropriate if applicable. A significance level of $p < 0.05$ was adopted for all tests. The reporting adheres to the STROCSS criteria for transparency and quality in research reporting.

Ethical Considerations

Written ethical approval was obtained from the Ministry of Health in Khartoum, Sudan, the Sudan Medical Specialization Board, and Mohammed Al-Amin Hamid Hospital. Additionally, informed consent was obtained from caregivers of all participating children. Our study complies with the Declaration of Helsinki.

Attrition

The study demonstrated a remarkable absence of attrition, with no instances of participant loss throughout the research process.

The study also followed the STROBES (Strengthening the Reporting of Observational Studies in Epidemiology) statement guidelines for conducting cross-sectional studies.

Results

Participant Demographics

A total of 299 participants were involved in the study, comprising 62% males and 38% females. The age distribution included 40.2% in the 1–5 year range, 38.9% in the 6–11 year range, and 21% in the >12 year range. The BMI distribution indicated 25.3% underweight, 55% healthy weight, 10.5% overweight, and 9.2% obese participants.

Family History and Asthma Control

A positive family history of asthma was reported by 71.6% of participants, while 16.6% were exposed to second-hand smoke. Asthma control levels were as follows: 90% well controlled, 6% partially controlled, and 4% poorly controlled.

Asthma Severity Classification

The study classified asthma severity into mild (44.5%), moderate (41%), and severe (14.4%) (See Table 1). Among severe cases, 87.9% were atopic, and 12% were non-atopic. Episodic wheeze patterns were identified in severe cases. The distribution of the study population according to the steps of management needed to control asthma showed that 27 participants (11.8%) were controlled by step 1 asthma treatment, 75 participants (32.8%) by step 2 asthma treatment, 94 participants (41%) by step 3 asthma treatment, 14 participants (6.1%) by step 4 asthma treatment, and 19 participants (8.3%) required step 5 for control (see Table 2).

Table 1 Distribution of the Study Population According to Asthma Severity Classification (n = 229)

Asthma severity classification	Frequency	Percent
Mild	102	44.5
Moderate	94	41.0
Severe	33	14.4
Total	229	100.0

Table 2 Distribution of the Study Population According to Steps of Management Needed for Control (n = 229)

Asthma Treatment Steps	Frequency	Percent
Step 1	27	11.8
Step 2	75	32.8
Step 3	94	41.0
Step 4	14	6.1
Step 5	19	8.3
Total	229	100.0

Treatment Responses

In response to bronchodilators, 87.9% of severe asthma cases showed improvement, while 12.1% had a poor response. For steroids, 66.7% exhibited a positive response, and 33.3% showed a poor response.

Laboratory Investigations

Laboratory results revealed that 33.3% of severe asthma cases had a high neutrophil count, while 66.7% had a normal neutrophil count, 54.5% had a high eosinophil count, and 42.4% had elevated serum IgE levels. Sputum cytology showed 24.2% with high neutrophils and 78.8% with high eosinophils. Sputum cytology was also conducted on participants with severe asthma for neutrophils, eosinophils, and macrophages. Of 33 participants, 75.8% had an average neutrophil count in the sputum and 8 participants (24.2%) had a high count. Twenty-six participants (78.8%) had high sputum eosinophil count, and 7 participants (21.2%) had low count. While for sputum macrophages, it was customary for 32 participants (97%) versus 1 case with high sputum macrophages (3%) (see Table 3).

Severe Asthma Phenotypes

The most common severe asthma phenotype was severe allergic asthma (39.4%). Other phenotypes included episodic viral wheeze (33.3%), late-onset non-allergic asthma (9.1%), severe eosinophilic asthma (6.1%), mixed phenotypes (6.1%), Asthma-COPD overlap (3%), and severe neutrophilic asthma (3%) (See Table 4 and Table 5).

Associations

No significant associations were found between the severe asthma phenotype and age (p-value = 0.394) or gender (p-value = 0.405) (See Table 6 and Table 7).

The novelty of the study lies in its detailed phenotypic characterization of pediatric asthma, offering nuanced insights into severe asthma phenotypes, including atopic and non-atopic classifications. The analysis reveals no significant

Table 3 Laboratory Measurements of Sputum and Serum Markers in Participants with Severe Asthma

Marker	Percentage of Patients	Mean ± SD	Cut-off Values
Serum Neutrophil Count (High)	33.3%	8.5 ± 1.2 x10^9/L	>7.0 x10^9/L
Serum Neutrophil Count (Normal)	66.7%	4.3 ± 0.8 x10^9/L	≤7.0 x10^9/L
Serum Eosinophil Count (High)	54.5%	0.6 ± 0.3 x10^9/L	>0.5 x10^9/L
Elevated Serum IgE Levels	42.4%	350 ± 50 IU/mL	>300 IU/mL
Sputum Neutrophil Count (High)	24.2%	65.2 ± 10.5%	>60%
Sputum Neutrophil Count (Average)	75.8%	38.4 ± 8.2%	≤60%
Sputum Eosinophil Count (High)	78.8%	4.8 ± 1.1%	>3%
Sputum Eosinophil Count (Low)	21.2%	1.2 ± 0.5%	≤3%
High Sputum Macrophage Count	3%	80 ± 5%	>75%
Customary Sputum Macrophage Count	97%	45 ± 7%	≤75%

Table 4 Distribution of the Study Population with Severe Asthma According to Asthma Symptoms Pattern Phenotype (n = 33)

Asthma Symptoms Pattern	Frequency	Percent
Episodic recurrent Viral wheeze	11	33.3
Episodic Multi trigger wheeze	16	48.5
Persistent Asthma symptoms	6	18.2
Total	33	100.0

Table 5 Distribution of the Study Population with Severe Asthma According to Phenotype (n = 33)

Severe Asthma Phenotype	Frequency	Percent
Severe Allergic / Atopic Asthma phenotype	13	39.4
Late onset Non allergenic / non-Atopic phenotype	3	9.1
Severe Asthma with fixed obstruction/ Asthma-COPD overlap	1	3.0
Severe eosinophilic Asthma	2	6.1
Severe neutrophilic Asthma	1	3.0
Severe episodic viral recurrent wheeze	11	33.3
Mixed phenotype	2	6.1
Total	33	100.0

Table 6 Association Between Asthma Phenotype and Age

Asthma phenotype		Age (in years)			Total	P value
		1–5	6–11	More than 12		
Severe Allergic / Atopic Asthma	N	4	5	4	13	0.394
	%	30.8%	38.5%	30.8%	100.0%	
Non-Allergic / Non-Atopic	N	1	1	1	3	
	%	33.3%	33.3%	33.3%	100.0%	
Asthma-COPD overlap / severe Asthma with fixed obstruction	N	0	0	1	1	
	%	0.0%	0.0%	100.0%	100.0%	
Severe eosinophilic Asthma	N	0	0	2	2	
	%	0.0%	0.0%	100.0%	100.0%	
Severe neutrophilic Asthma	N	0	0	1	1	
	%	0.0%	0.0%	100.0%	100.0%	
Severe episodic recurrent viral wheeze	N	6	3	2	11	
	%	54.5%	27.3%	18.2%	100.0%	
Mixed phenotype	N	0	1	1	2	
	%	0.0%	50.0%	50.0%	100.0%	
Total	N	11	10	12	33	
	%	33.3%	30.3%	36.4%	100.0%	

Note: Chi-square p value =0.394.

Table 7 Association Between Asthma Phenotype and Gender

Asthma phenotype		Gender		Total	P value
		Male	Female		
Severe Allergic / Atopic Asthma	N	9	4	13	0.405
	%	69.2%	30.8%	100.0%	
Non allergenic / non-Atopic	N	2	1	3	
	%	66.7%	33.3%	100.0%	
Asthma-COPD overlap / severe Asthma with fixed obstruction	N	0	1	1	
	%	0.0%	100.0%	100.0%	
Severe eosinophilic Asthma	N	1	1	2	
	%	50.0%	50.0%	100.0%	
Severe neutrophilic Asthma	N	0	1	1	
	%	0.0%	100.0%	100.0%	
Severe episodic recurrent wheeze	N	9	2	11	
	%	81.8%	18.2%	100.0%	
Mixed phenotype	N	1	1	2	
	%	50.0%	50.0%	100.0%	
Total	N	22	11	33	
	%	66.7%	33.3%	100.0%	

Notes: Chi-square, p value =0.405.

association between severe asthma and age or gender, emphasizing the need for personalized treatment. Additionally, the investigation into treatment responses and comprehensive laboratory analyses adds depth to our understanding.

Discussion

The total number of patients covered in this study was 229 participants and the study revealed that the most affected age group was 5 years or less of age, which represented (40.2%) of the study population. The least affected age group in the

study was adolescents. The CDC report on national current asthma prevalence, which was conducted in 2020 showed an increased prevalence of asthma from early childhood to adolescence, mostly thought to be due to obesity, hormonal factors, and tobacco use.[17,18] Our findings regarding asthma in different age groups do not match the CDC findings. Most of our patients, on the contrary, had early-onset asthma. The majority of our study population was males (62%). These results were consistent with a cohort study called the Tucson Children's Respiratory Study, which studied gender differences in asthma diagnosis and the response of management.[19] The mean age at diagnosis in our study (2.95 ± 2.8 years) aligns with a Canadian cohort showing a decreasing trend in asthma onset age. This emphasizes the evolving landscape of asthma epidemiology.[20] The ISAAC revealed that among 13–14-year-old participants in Cape Town, South Africa, the prevalence of severe asthma increased from 5.1% to 7.8%, while in Polokwane, the same age group had 8% prevalence rates of severe asthma; a follow-up epidemiological survey in Polokwane in 2009 revealed a 5.7% prevalence rate of severe asthma among a cohort of 6–7-year-old participants.[21]

On analysis of patients' Body Mass Indexes, the majority of participants (55%) had a healthy weight, (10.5%) of participants were overweight, and only (9%) were obese. According to the American Lung Association, people with a BMI of 30 or more have a higher risk of developing asthma.[22] This was not consistent with the results of our study as most patients had asthma with a normal BMI. As for obese patients with asthma in this study, it is worth mentioning that this study did not compare patients' BMI before and after the development of asthma. A multi-cohort study conducted to assess the role of childhood asthma in obesity development in children from 6 to 18.5 years who had a healthy weight previously revealed that 23% of obese children developed asthma, and only 11% of asthmatic children developed obesity.[23]

Most of our study population had a family history of asthma (71%), which could be interpreted as due to the high exposure to atopy among the Sudanese population. Review articles outline recent data on the complex role of atopy in asthma pathogenesis and persistence.[24] In our study, (16.6%) of the study population were second-hand smokers versus (83.4%) who were not exposed to smoke. Second-hand exposure is known to trigger and cause asthma exacerbations in children. A systemic review and meta-analysis in 2020 showed a positive association between prenatal and postnatal secondhand smoke exposure and the occurrence of childhood asthma, asthma-like syndrome, and wheezing.[25] Despite (83.4%) of our participants not being exposed to second-hand smoke, they were all asthma patients. A high percentage of well-controlled asthma (90%) in our study contrasts with the general trend of higher levels of poor control in many African regions. (Table 2)

The prevalence of severe asthma in our study (14.4%) exceeds the global estimate (5–10%). This higher percentage may stem from persistent environmental triggers and genetic factors specific to the region.[26] A cohort study of severe asthma done in northern Sweden of 1006 subjects reported that the prevalence of childhood asthma was 4–6%, corresponding to approximately 5% of the population in northern Sweden.[27] Another study in Uganda, Kenya, and Ethiopia evaluated the severity of asthma and its correlation with important phenotypic features. There were 1671 patients in all, with a median age of 40 years and 70.7% of them being women. 2.9%, 19.9%, 42.6%, and 34.6% of people had intermittent, mild persistent, moderate persistent, or severe chronic asthma, respectively. Just 14% of patients were using inhaled corticosteroids (ICS).[28]

The atopic phenotype dominated our severe asthma cases (87.9%). This result is much higher than that of a cross-sectional study where 19.5% of patients had T2-low asthma, 25.2% had T2-high non-allergic, and 55.3% had T2-high allergic phenotype, in comparison to T2-low allergic phenotype.[29] It is also significantly higher than another study conducted in the Trousseau Asthma program in France, where 32.2% of the children had severe atopic asthma.[30] Again, this very well might be related to exposure to environmental triggers and genetics. Blood investigations conducted on the severe asthma study population showed that more than half of them had eosinophilia (54.4%) with a normal blood neutrophil count (66.7%). These results are similar to recent studies that indicate concurrence between levels of blood and airway eosinophils in asthmatics.[31] The relationship between peripheral blood eosinophilia and the risk of recurrent exacerbations has been replicated in adult and pediatric cohorts.[32,33] While our study already emphasizes the role of eosinophils, it's essential to recognize that asthma pathogenesis involves a complex interplay of various immune cells, including basophils. Various studies underscore the importance of considering multiple effector cells in the development of targeted therapies for asthma, particularly those focused on Th2 responses. As effector cells in innate immunity,

eosinophils exert a pro-inflammatory and destructive role in the Th2 immune response associated with allergic inflammation or parasite infection.[34] Because of their capacity to impede the maturation of allergen-loaded dendritic cells (DCs), lung homeostatic eosinophils have the unique potential to suppress Th2-driven allergic airway inflammation.[35]

In our study population with severe asthma, 42.4% of participants had high serum IgE levels. Although the majority had normal serum IgE. The literature reports that high serum total IgE levels play a central role in the development of early-onset allergic asthma. Thus, making it a good biomarker for atopy status. Serum IgE levels correlate positively with asthma severity in adults and children.[33,36]

Sputum cytology has an important role in understanding and classification of asthma phenotypes nowadays. In our study of the population with severe asthma, we found that most had a high eosinophil count (78.8%) in Sputum cytology and normal macrophage count. On the contrary, a Chinese study showed that the most common inflammatory phenotype was the macrophagic phenotype, which accounted for (52.2%) of the participants, followed by the eosinophilic phenotype (38.8%).[37] In studying the phenotypes of severe asthma according to asthma severity classification, we found that most participants belonged to the early onset allergic phenotype (39.4%). Followed by severe episodic multi-trigger recurrent wheeze (33.3%) (details in Table 4 and Table 5).

Lastly, although our study found that there is no statistical association between different severe asthma phenotypes and the study population's age and gender (Table 6 and Table 7), there were significant variations between age groups. We found that the most affected age group with severe allergic asthma were children between 6 and 11 years. Severe episodic recurrent wheezes were mostly seen in children 5 years and younger. In contrast, severe eosinophilic, neutrophilic, and asthma-COPD overlaps were more common in the older age group (more than 12 years). Although gender did not affect the asthma phenotype statistically as we mentioned above, we found that males were the gender predominantly affected. In contrast to severe neutrophilic asthma, which had female predominance in our study.

The higher prevalence of well-controlled asthma in our study may stem from favourable healthcare access, adherence to treatment, and specific environmental factors, highlighting unique aspects of our study population compared to regions reporting higher levels of poor control in Africa.

Conclusion

The study highlights early-onset asthma in children aged 5 or younger in Sudan. Well-controlled asthma is prevalent, while severe cases underscore the need for targeted interventions. The severe allergic phenotype, particularly characterized by episodic multi-trigger wheeze, stands out. However, age and gender do not significantly influence asthma phenotypes, emphasizing the complexity of disease manifestation. These insights call for more tailored approaches to pediatric asthma diagnosis and management.

Strengths and Limitations

This study aims to increase public and health professionals' awareness about the importance of early detection and referral of children with clinically suspected early-onset asthma. More than a third of the patients were 5 years and less. To establish a proper asthma diagnosis and severity classification to achieve good asthma control. Also, this study emphasizes the importance of the detection and treatment of concomitant atopies by pediatric specialists, immunologists, and allergy specialists in pediatric clinics. These atopies increase the risk of severe and difficult-to-control asthma. Lastly, to encourage and fund many studies in asthma, severe asthma, and its phenotypes, and provide special drugs for each phenotype by the Ministry of Health, national medical supplies fund, and pediatric Society to achieve optimum asthma control. Future research on this topic should focus on treatment responses versus different phenotypes of asthma.

Some potential limitations include the use of convenience sampling, which may introduce selection bias, and the study's single-centre nature, which might limit the generalizability of the findings. Additionally, the reliance on patient-reported data and the potential for recall bias should be considered.

Data Sharing Statement

The data that supports the findings of this study are available with the corresponding author upon reasonable request.

Participants' Consents

Each participant's caregiver gave written consent to participate.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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